Poly(ethyl glycol) Assisting Water Sorption Enhancement of Poly(ε-caprolactone) Blend for Drug Delivery

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ABSTRACT: Poly(ε-caprolactone) (PCL) has been thermally synthesized, and then fractionated to blend with poly(ethyl glycol) (PEG). Blend films of PCL and PEG have been prepared by solution casting. Fourier transform infrared spectrum and differential scanning calorimetry of the films have been carried out, and the results indicate some hydrogen bonding interaction between the two components, which is resulted from the carbonyl groups of PCL and the hydroxyl end-groups of the low-molecular-weight PEG. Scanning electron microscope images of the blend films reveal porous network structures for their surfaces and for their inner parts and the porous structure becomes more pronounced with the increase of PEG in the blend film. Ibuprofen (IBU) was used as the model drug to test the drug release behavior for the PCL/PEG blend matrices. The results show that IBU could be released from the blend tablets rapidly, and the release rate increases with PEG content. Analysis of the release profiles indicates PCL erosion control release mechanism of pure PCL tablet, but drug diffusion control of the blend tablet, because PEG can absorb water to allow water feasible to diffuse into drug core and dissolve drug. Therefore, the interconnected channels in the blend matrices and the hydrophilic nature of PEG contribute to the improvement of the IBU release rate. The research indicates that drug release rate from PCL based material could be efficiently improved by addition of small amount of hydrophilic low-molecular-weight PEG. © 2011 Wiley Periodicals, Inc. J Appl Polym Sci 122: 2309–2316, 2011

Key words: poly(ε-caprolactone); poly(ethyl glycol); blend; water sorption; drug release; improvement

INTRODUCTION

Poly(ε-caprolactone) (PCL), an officially approved synthetic polymer usually applied in biomedical fields, is receiving increasing attention due to its excellent biocompatibility and degradability.[1] As a fascinating biomedical material, PCL is widely used in drug-delivery systems or in tissue engineering.[1–8] However, the polymer shows slow biodegradation and drug-release rates *in vitro* as well as *in vivo* because of its high crystallinity and strong hydrophobicity, which seems to limit its applications.[9–13] To improve the hydrophilicity of the final material, polar parts can be introduced into the macromolecule. One way is to prepare PCL based copolymers.[1,14–21] For examples, poly(ethylene glycol) (PEG) precursors have been introduced into backbone of PCL chain to obtain random block copolymer,[14] diblock copolymer,[15] triblock copolymer with PEG the inner block,[16,17] or with PCL the inner block,[18] and so on, which have been successfully used as drug delivery carries. Another method is to physically mix PCL with hydrophilic sources, which can either be inorganic material[22] or be organic polymers.[23,24] By a simple and convenient technique of blending, it is convenient to prepare PCL materials with advanced functions. Among the many possible polymers to mix with PCL, PEG, another FDA-approved biodegradable and biocompatible polymer, has been extensively used as drug carrier due to its capability to improve the wettability and solubility of water insoluble drugs.[25,26] Recently, Guo et al.[27] prepared PEG/PCL blend implants by a combination of twin-screw mixing and hot-melt extrusion to load high content of praziquantel, which can be released from the blend matrices steadily *in vitro* and *in vivo*. Moreover, PCL/PEG blends could be prepared by solution casting method through dissolution of the two polymers in cosolvents.[28,29] It has been found that phase separation occurred in the blends when the PEG had molecular weight higher than 4000 g/mol and the content higher than 5 wt %. The PEG have formed spherical dispersed phase, some of which could be leached out in aqueous medium to form pores in PCL matrices. The formed

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pores in the tablets would benefit for the diffusion of water into the drug core, and would speed up the theophylline release from the tablets coated with the PCL/PEG blends.[28] To obtain highly porous tablet for faster drug release, the content of PEG in PCL and PEG blends was always kept higher than 10 wt %.

In this article, a PEG with a low molecular weight of 1500 g/mol was applied to prepare PCL/PEG blends, and its content was less than 10 wt %. Because of the hydroxyl end-groups of the low-molecular-weight PEG and of its low content, the microstructure of the blend would vary from those reported.[27–29] At the same time, the low-molecular-weight PEG would absorb water and would be dissolved faster in water than high-molecular-weight PEG, so that speeding up of drug release from the present PCL/PEG blend would be expected. Therefore, blend films of PCL and low-molecular-weight PEG were prepared by solution casting method. Fourier transform infrared spectra (FTIR), differential scanning calorimetry (DSC), and X-ray diffraction (XRD) measurements of the films have been performed to analyze the interaction between the components in the blend films. The microstructures and the water sorption (WS) behaviors of the films were studied to know their contributions to the drug release. The release behaviors were determined when IBU was loaded in the blend tablets, and the release mechanisms have also been suggested.

EXPERIMENTAL

Materials

By the addition of catalyst of stannous octoate, commercial ε-CL (99%, Aldrich) was applied without purification to thermally polymerize at 140°C in a nitrogen atmosphere for 14 h. The obtained product was dissolved in toluene to have a concentration of about 1 wt %, then methanol was added dropwise with stirring until turbidity of the mixture solution. After that, the precipitated phase was filtered off and washed with water, and dried under vacuum at ambient temperature. According to $[\eta] = 2.66 \times 10^{-2}.M_{\eta}^{0.71}$,[30] the viscosity-average molecular weight (M_η) of thus obtained PCL was determined in tetrahydrofuran at 25°C to be 3.7×10^4 g/mol by viscometry. Dihydroxyl-terminated PEG (analytical grade) with a number-average molecular weight of 1500 g/mol was purchased from Chinese Medicine Group (Shanghai, China). Ibuprofen (IBU) was purchased from Hubei Baike Hengdi Medicine (Hubei, China). All other reagents were analytical grade and were used as received. Phosphate buffer solution (PBS, 0.1 mol/L, pH = 7.4) was prepared according to the known method.[31]

Preparation

PCL and PEG with different weight ratios were dissolved in dichloromethane to have a polymer concentration of 5 wt %, then the obtained solutions were cast into Petri dishes, respectively. After solvent evaporation at ambient temperature and dried under vacuum to constant weight, desired films were obtained. The films were coded as PCL-PEGm, with the number m being the percentage of PEG contained in the samples, such as 1, 3, and 5 wt %.

PCL, PEG, and IBU were mixed in solution, and was added dropwise to a steel container. The solvent was evaporated at ambient temperature, and dried under vacuum to constant weight. The PEG contents in the obtained solid tablets were 1, 3, or 5 wt %, while that of IBU was kept constant to be 5 wt %. The tablet samples extracted from the container were obtained to have 6.2 mm in diameter and 3.0 mm in thickness, which were used to test their drug release behaviors.

Measurements

FT-IR characterizations of the films were recorded with a Nicolet Avatar 360 instrument (Nicolet, Madison, WI) at 25°C. The test specimens were prepared by first cutting the films into small particles, and then were vacuum-dried at 40°C for over 48 h to mix with KBr to produce disks for the measurements.

DSC analyses for the films were performed on a Netzsch DSC 204 under nitrogen atmosphere at a heating speed of 10°C/min from RT to 350°C. XRD was carried out by using a PANalytical X'Pert PRO diffractometer (PANalytical, Netherlands) with CuKα radiation. The films were continuously scanned from10° to 50° (2θ) at a speed of 0.0167°/s.

The film or tablet specimens were frozen in liquid nitrogen, and snapped immediately, then vacuum-dried. The free surface (side in direct contact with air when solvent evaporating during preparation), back surface (bottom side contact with container) and cross section of the fractured films were coated with a thin layer of gold (about 2 nm) to observe their microstructures by using an XL30 scanning electron microscope (ESEM-TMP, Holland) with 20 kV accelerating voltage.

Drug release

The drug release was carried out according to a standard method suggested in literature.[31] The IBU containing tablet samples were respectively, immersed in 900 mL PBS solution at 37 ± 0.5°C with stirring at a rate of 100 rpm. After desired time of drug release, 5 mL of the medium solution was taken out to measure the absorption at wavelength

of 222 nm by using an UV detector (Beckman DU-7400) to calculate the release amount of IBU. At the same time, 5 mL of fresh PBS buffer was added into the release vessel. The absorption of IBU at 222 nm is maximum.[16]

The blend films were soaked in PBS to determine their WS. After desired time, the specimen was taken out to remove the water on the surface with filter paper. The WS was calculated by

$$\mathrm{WS} = \frac{W_2 - W_1}{W_1} \times 100\% \quad (1)$$

in which W_1 is the original weight of the film, and W_2 the weight of the film after water up-taking.

RESULTS AND DISCUSSION

Miscibility

The FTIR spectra of the films prepared from pure PCL, pure PEG and their blends have been recorded, as shown in Figure 1. The curves of pure component films show typical spectra of pure PCL and of pure PEG, respectively. Figure 1(B) shows the spectra between 1400 and 2400 cm^{-1}, corresponding to the stretching vibration of carbonyl groups of PCL. The sharp peak centered at 1726 cm^{-1} corresponds to PCL in its crystalline conformation.[32,33] When blending with PEG, no appreciable shift of the peak at 1726 cm^{-1} has been observed. However, another band develops at about 1703 cm^{-1}, which is attributed to the hydrogen-bonded carbonyl groups. It is more pronounced as the increase of PEG content, suggesting possible interaction between the two components in the blends.

Figure 2 shows the DSC thermograms of pure PCL film and of the blend films. The maximum of the DSC curve was considered to be the melting temperature of PCL, T_m. The T_m of pure PCL is 64.4°C, and is in good agreement with those reported in literatures. It is interesting to note that there are two obvious melting peaks in the thermogram of PCL-PEG1, which are located at temperatures slightly deviated from that of pure PCL. A wide stage other than peak for PCL-PEG3, and a peak together with a shoulder for PCL-PEG5 have been found in their thermograms. The T_m of the used PEG with a molecular weight of 1500 g/mol is reported to be 49.6°C.[27] The fusion of PEG has not been observed in the DSC thermograms due to its low content, so the peaks, stage or shoulder in the thermograms are attributed to the fusion of PCL in the blends. Double melting-peaks of PCL in blends have been found in compatible and in partially compatible systems.[34–37] Guo et al.[37] have prepared blends of low-molecular-weight uncured poly(ethylene glycol)-type epoxy resin (PEG-ER) and PCL to discover double melting peaks of PCL in the DSC thermograms. The double melting-peaks of PCL were claimed to be caused by the recrystallization of PCL and subsequent melting,[36,37] resulting from the miscibility of PEG-ER and PCL. Therefore, the melting variation of PCL in the present blends suggests partially compatible of the components, which is consistent with the results obtained from FT-IR. The compatibility of PCL and PEG might be due to hydrogen-bonding interaction between the carbonyl groups of PCL and the hydroxyl end-groups of PEG. Lin et al.[28,29] claimed some interactions but impossible of hydrogen bonding between PCL and PEG. In their studies, they might have used nonhydroxyl terminated PEG. But in this work, the PEG is hydroxyl terminated, and its molecular weight is 1500 g/mol,

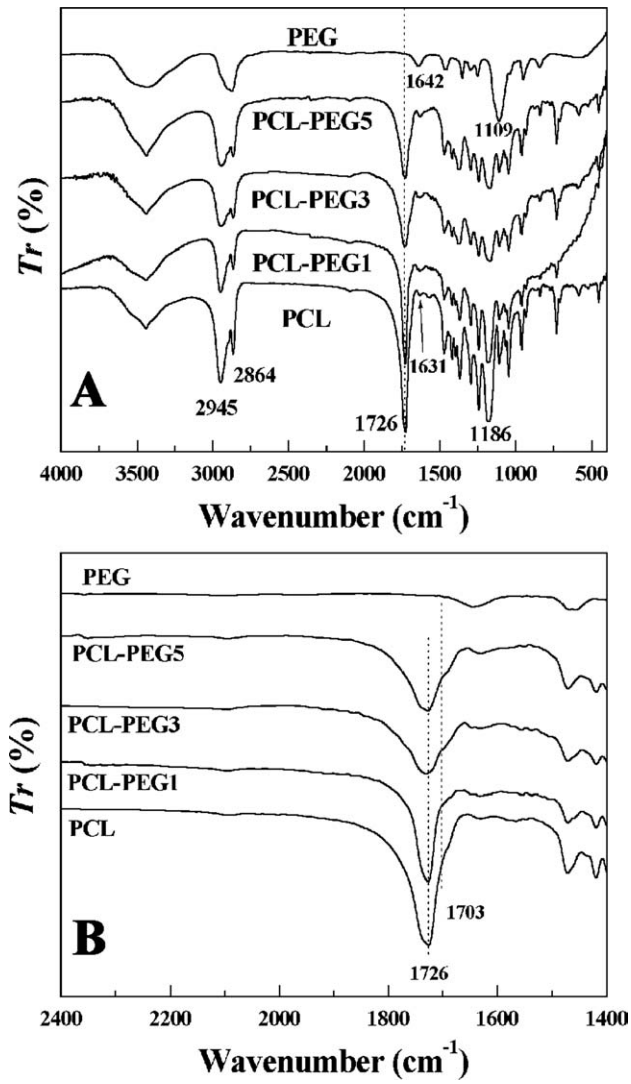

Figure 1 FT-IR spectra (A) of the films prepared from pure PCL, pure PEG and their blends, and the magnified part ranging from 1400 to 2400 cm^{-1} (B). The dotted lines are located at 1726 and 1703 cm^{-1}, respectively.

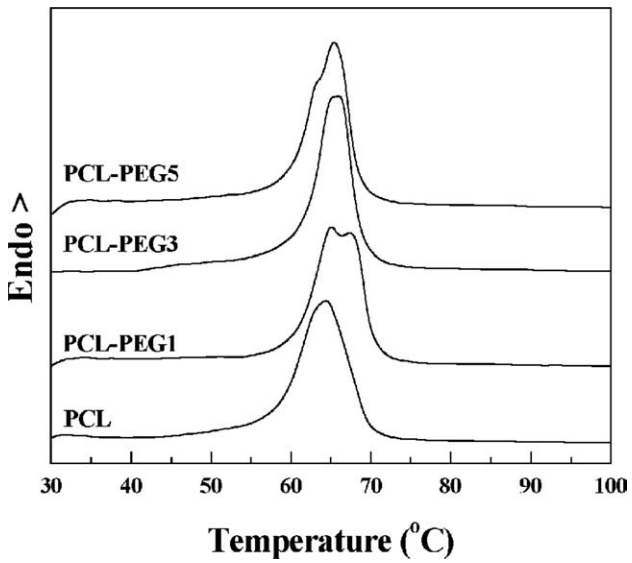

Figure 2 DSC thermograms of the films.

so that it can supply many hydroxyl groups to hydrogen bond the carbonyl groups of PCL.

The degree of crystallinity of PCL, χ_c(PCL), was calculated by the following equations:

$$\chi_c(\text{blend}) = (\Delta H_f - \Delta H_c)/\Delta H_f^0 \quad (2)$$

$$\chi_c(\text{PCL}) = \chi_c(\text{blend})/w(\text{PCL}) \quad (3)$$

where χ_c(blend) is the crystallinity degree of the blend material, $\Delta H_f^0 = 136$ J/g is the heat of fusion of 100% crystalline PCL,[38] and w(PCL) is the weight fraction of PCL in the blend. In the equation, ΔH_f is the heat of fusion of the blend, which can be integrated from the endothermal peak and $\Delta H_c = 0$ is the heat of crystallization during the same heating scan due to the absence of crystallization exotherm in the DSC thermograms. The χ_c(PCL) for pure PCL film is 22.6%, and those for PCL-PEG1, PCL-PEG3, and PCL-PEG5 PCL-PEG10 are 19.4, 18.8, and 19.2%, respectively. Thus, the deviation of T_m is considered to be the result of crystallinity variation of PCL in the blends, which is affected by its interaction with PEG. Those were further confirmed by the XRD results of the films, which is shown in Figure 3. The pattern of pure PCL reveals two diffraction peaks at $2\theta = 21.4^\circ$ and 23.7°, and the patterns of the blend films are similar as that of pure PCL. At the same time, the diffraction peaks of PEG at 2θ around 18.6° and 23.3°[39] are hardly observable, indicating that the crystallization of PEG has been restrained in the blend. The peak intensities for PCL diffraction in the blend films are lower than those of pure PCL, implying the lower crystallinity of PCL in the blend film. It is known that miscible components in polymer blend will interfere with each other crystallization, leading to decrease of crystallinity. Therefore, the results also indicate interaction between the PCL and the hydroxyl-terminated low-molecular-weight PEG.

Microstructure of the blends

Figure 4 shows the SEM images of the free surface (left) and back surface (right) for PCL, PCL-PEG3, and PCL-PEG5, respectively. Both the free surface and the back surface reveal network structures, irrespective of pure PCL or blend films. However, the free surfaces are much coarser than the back surfaces, which might be due to the fast solvent evaporation at the free surface. With the addition of PEG, the network structures in both free surface and back surface become more obvious, and the channels in the network structure turn larger with the increase of PEG content in the film. The SEM images of the inner parts of PCL and PCL-PEG5 are shown in Figure 5. The inner part of PCL reveals smooth and dense structure, while that of blend film exhibits porous morphology. However, no obvious phase separation in the blend film of PCL-PEG5 has been found in the SEM image, even observed by a high magnification with a factor of 10, 000 (picture not shown). This is possibly due to the above-mentioned compatibility between PCL and PEG. From the SEM observation, it is striking that a common character of more interconnected channels has been found in the blend films. When PEG was introduced in the PCL solution, the interfacial tension of the solution would decrease. After evaporation of solvent for some time, the film started to shrink. Due to the lower surface tension of the blend polymer solution, the shrinking of the blend would be greater than that of pure PCL, resulting in the more pronounced porous network

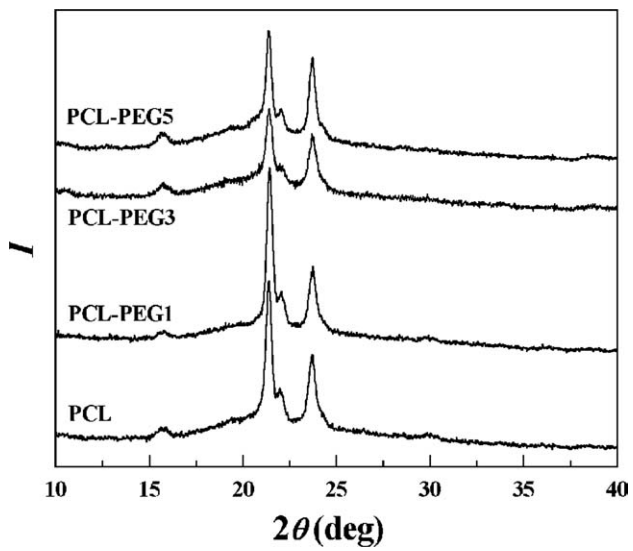

Figure 3 XRD patterns of the blend films.

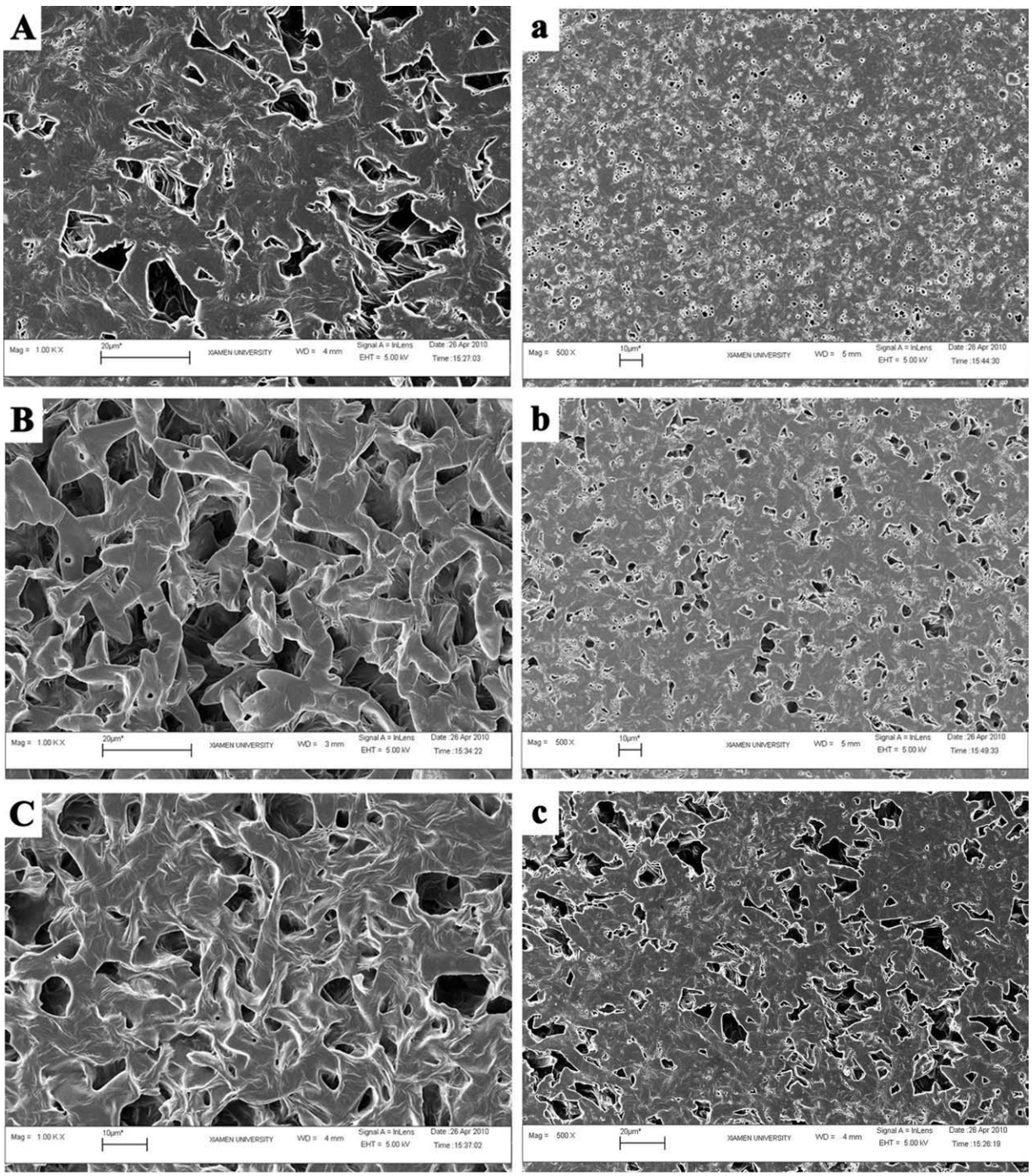

Figure 4 SEM images of the free surface (left) and back surface (right) for PCL (A and A1), PCL-PEG3 (B and B1) and PCL-PEG5 (C and C1), respectively.

morphology of the blend films. The interconnected channels are of great benefit to the diffusion and penetration of drug release medium.[29]

Drug release

An semiempirical model[40–43] is often used to describe Fickan and non-Fickan drug release from polymer matrices, which reads

$$\frac{M_t}{M_\infty} = K \cdot t^n \tag{4}$$

where M_t is the amount of drug released at time t, M_∞ is the amount of drug released after infinite time, K is a constant, which takes into account structural and geometric features of the matrix, and n is a release exponent indicative of the mechanism by which drug is released.

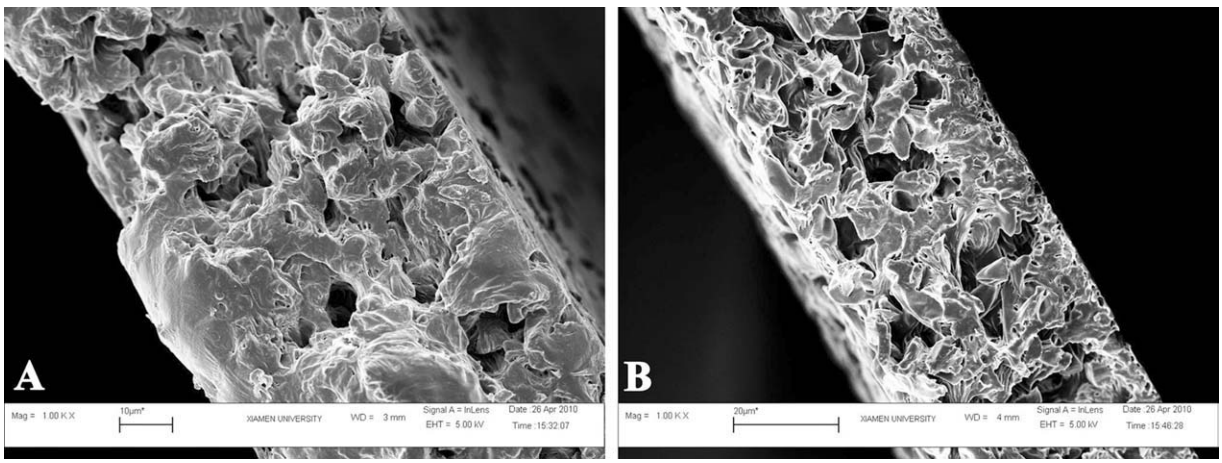

Figure 5 SEM images of the inner structure of PCL (A) and PCL-PEG5 (B).

Figure 6 shows the releases of IBU from pure PCL tablet and from the blend tablets, which were prepared by the same procedure as film preparations. The release data were further fitted by eq. (4), and the related K and n values are listed in Table I, respectively. It is observed that IBU can be released from all the polymer matrices gradually. However, the release rate of IBU from blend tablets is significantly improved. The release rate constants K for the blend tablets are much greater than that of pure PCL, and the value increases with the increase of PEG content in the blend, indicating more pronounced porous microstructure, which is in good agreement with the phenomenon observed by SEM. Meanwhile, the releases of IBU from PCL-PEG3 and PCL-PEG5 are similar, and the K values are very close, indicating that the value does not increase linearly with PEG content. It is reported that interconnected channel structure plays important role on the drug release rate,[29] so the similar network structures of PCL-PEG3 and PCL-PEG5 might be responsible for the close K values. The possible drug release mechanism from the tablets was further evaluated by the n values. As shown in Table I, the n of pure PCL is 0.96, and the release shows an almost linear profile, indicating an erosion of the PCL matrix to control the release mechanism, because PCL can be hydrolytically degraded through breaking ester functional groups.[44] The n value decreases with the increase of PEG content in the blend film, suggesting that the drug release mechanism shifted from PCL erosion control for pure PCL tablet to drug diffusion control for blend tablets.[40–43]

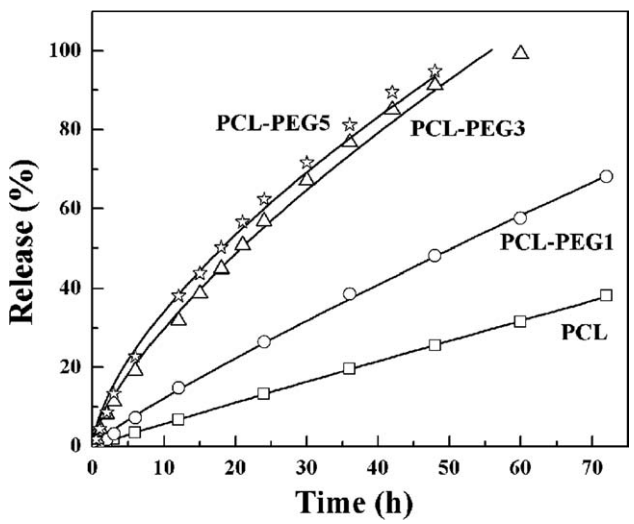

Figure 6 The release of IBU from PCL and PCL/PEG blend matrices. The lines were the best fits of each set of data points by eq. (4).

It can be understood that water diffusion and penetration into drug core to dissolve drug is the key step of drug release from polymeric matrices. As a hydrophilic polymer, PEG in the present blend tablets will absorb water, and then be swollen and be dissolved in an aqueous medium, which will be helpful for the release of the drug release. Therefore, the WS behaviors of the films were determined, with the results shown in Figure 7. For pure PCL film, the WS increases slowly, and reaches an almost maximum of 6% in 60 min. After that, the WS of pure PCL film seems decreases a little. This is understood that the WS at the beginning stage might be due to the physical adsorption by the channels in the PCL film, and the slow decrease in the later stage be due to the degradation of PCL in the medium.[9,44] The WS behaviors for the blend films show

TABLE I
Values of Parameters K and n

Sample	K (%/h)	n
PCL	0.63	0.96
PCL-PEG1	1.64	0.87
PCL-PEG3	5.93	0.70
PCL-PEG5	6.71	0.69

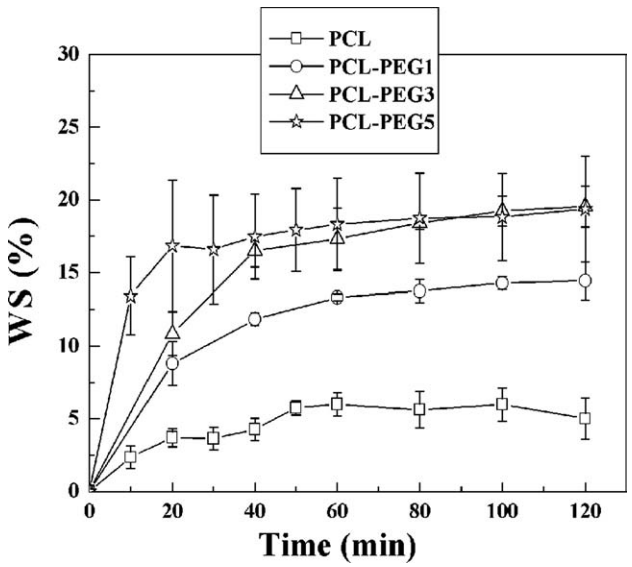

Figure 7 Water sorptions of the films. Each point represents the mean ± S.D. ($n = 3$).

similar tendency as that of pure PCL. However, the blend films exhibit much higher and faster WS. With only 1% PEG addition, the blend film of PCL-PEG has a WS of higher than 13% in 60 min and the WS speed at the beginning stage is much higher. The WS speed increases with the increase of PEG content in the blend film. The WS values after 60 min aqueous medium soakage of PCL-PEG3 and PCL-PEG5 are 18 and 20%, respectively. The much higher WS of blend film than that of pure PCL is thought to be caused by the network structure of blend film and by the hydrophilic nature of PEG. The WS of the blend films increases constantly, and the absorption rates are slower after 20 min. Meanwhile, no obvious decrease of WS has been found for blend films. Because of the hydrophilic nature of PEG, the blend films would take water continually, which would stay in the inner channels of the matrices. Although the erosion of PCL and dissolution of PEG in the blends, the absorbed water in the channels would be heavier to result in the WS increasing. Therefore, the absorbed water would help to dissolve drug, and would benefit the following diffusion of drug to improve drug release. At the same time, the low amount of WS for pure PCL would slow down the drug release rate, because the embedded drug could only be released out after the erosion of the PCL at the surface of the channels in the matrix.

The above analyses were further evidenced by the microstructure changes of the blend tablets. Figure 8 shows the SEM images of PCL-PEG5 after water extraction (A) and after IBU release (B) for the same time of 24 h, respectively. After water extraction, PEG was leached out, resulting in the sponge like microstructure of the material. The tablet after drug release reveals similar microstructure as that after water extraction. This result indicates that the drug release from blend tablet might be similar as the leaching of PEG from the blend. It is thus believed that the hydrophilic PEG was dissolved together with IBU during the release processes. Moreover, the dissolution of PEG could result in porous microstructure of the blend tablet, which allowed water feasible to diffuse into drug core and dissolve IBU. Therefore, the presence of PEG in the tablet matrix would improve not only WS, but also the drug release rate, which is consistent with the drug release mechanism suggested above.

CONCLUSIONS

Blend films of PCL and PEG have been prepared by solution casting. FTIR, DSC, and XRD results indicate some hydrogen bonding interaction between the two components, which is resulted from the

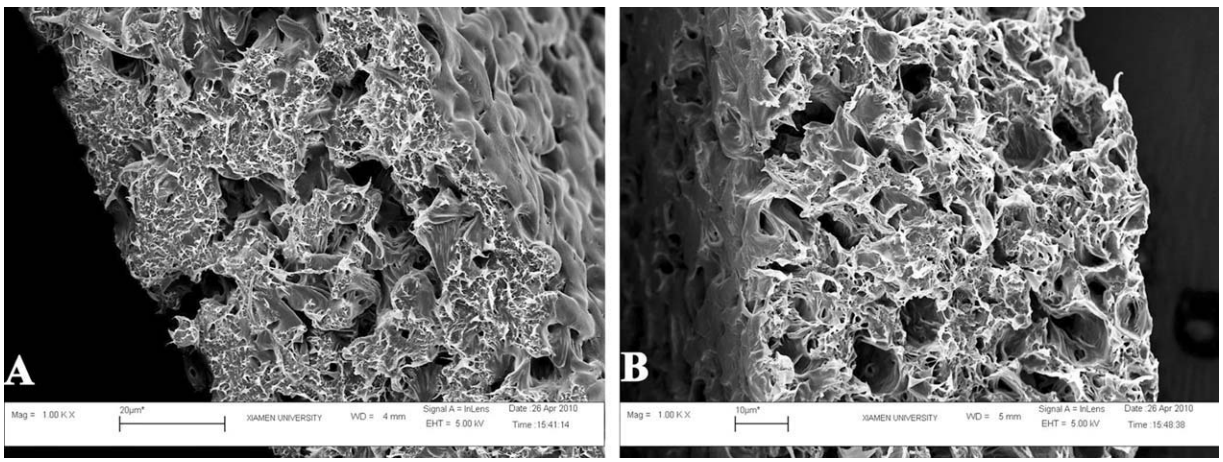

Figure 8 SEM images of PCL-PEG5 after water extraction (A) and after IBU release (B) for the same time of 24 h.

carbonyl groups of PCL and the hydroxyl end-groups of the low-molecular-weight PEG. The surface and the inner parts of the blend films show porous network structure, which becomes more pronounced with the increase of PEG content in the blend films. The interconnected channels in the network structured blend films are beneficial to WS of the materials, and to the drug release. The model drug IBU can be released from the blend tablets rapidly, and the release rate increases with PEG content. Analyses of the release profiles of the tablets suggests a release mechanism shift of an PCL erosion control for pure PCL tablet to drug diffusion control for blend tablet. The hydrophilic nature and fast dissolution character of the low-molecular-weight PEG contribute to the improvement of the IBU release, because it can absorb water to allow water feasible to diffuse into drug core and dissolve drug. Therefore, this work suggests that a small amount of low-molecular-weight PEG could be added in PCL matrix to evidently speed up drug release from the material.

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